UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/571,012	03/08/2006	Frank Cuttitta	4239-82094-06	4600

36218 7590 06/10/2010

KLARQUIST SPARKMAN, LLP
121 S.W. SALMON STREET
SUITE #1600
PORTLAND, OR 97204-2988

EXAMINER	
PAGONAKIS, ANNA	
ART UNIT	**PAPER NUMBER**
1628	

NOTIFICATION DATE	DELIVERY MODE
06/10/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

tanya.harding@klarquist.com
docketing@klarquist.com

Office Action Summary	Application No.	Applicant(s)	
	10/571,012	CUTTITTA ET AL.	
	Examiner	Art Unit	
	ANNA PAGONAKIS	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *80,81,90-97 and 99* is/are pending in the application.

4a) Of the above claim(s) *91 and 99* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *80,81,90 and 92-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed 5/24/2010 has been received and entered into the present application.

Applicant again requests rejoinder alleging that the generic compound described in the '750 patent does not encompass the instantly claimed compound XV'. This not found persuasive. The reasons for maintaining the lack of unity mailed on 8/18/2009 has been set forth in the Office Action mailed 2/22/2010. The requirement is deemed proper and is therefore made final.

Applicant's arguments filed 5/24/2010 have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 78-82, 84-90 and 92-97 are rejected under 35 U.S.C. 112, first paragraph, because the specification while enabling for the treatment of lung cancer, does not reasonable provide enablement for a method of inhibiting an activity of a gastrin release peptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is mostly nearly connected, to make and use the invention in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;

2) the breadth of the claims;

3) the predictability or unpredictability of the art;

4) the amount of direction or guidance presented;

5) the presence or absence of working examples;

6) the quantity of experimentation necessary;

7) the state of the prior art; and,

8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

The presently claimed invention is drawn to a method of inhibiting an activity of a GRP peptide, as well as treating a disease or disorder associated with inhibition of GRP, such as cellular proliferative diseases, comprising contacting the peptide with an effective amount of a pharmaceutical composition comprising a compound of formula XV.

The instant specification as originally filed lacks adequate guidance, direction or discussion to apprise the skilled artisan how the claimed compound may be used to achieve (1) the inhibition of GRP activity and (2) the disclosed utilities for treating conditions wherein GRP inhibition has been implicated and particularly how it is implicated in the treatment of cellular proliferative diseases, with at least a reasonable expectation of successfully achieving the treatment of the same. The instant specification fails to present any evidence, either in the form of data or scientifically sound reasoning, which would provide such a reasonable expectation that the claimed compounds would have been effective for the inhibition of GRP as well as disclosed disorders, including cellular proliferative diseases associated with the inhibition of GRP. Though it is noted that Applicant need not necessarily demonstrate the precise manner in which the claimed therapeutic agent(s) ameliorate a particular disease state, such a mechanism must be elucidated in cases where Applicant relies upon a correlation between the particular activity of a compound and a reasonable expectation of efficacy in treating a particular disease.

The instant specification states, repeatedly, that “modulatory" agents were identified for AM and GRP (page 16, line 20). Further, the specification discloses "without wishing to be bound by any particular mechanism, the inventors appear to have confirmed this assumption by the identification of biologically active compounds capable of modulating the physiology of AM and GRP" (page 17, lines 3-6). Table 1 on pages 18-19 of the specification disclose "compound that induced consistent effects on *modulating* second messenger activation by AM or GRP..." (emphasis added).

The examples provided by Applicant are drawn to primary screening for AM and GRP (Example 3, page 33); analysis of second messengers including cAMP analysis for AM and GRP as well as IP_3 and Ca^{2+} analysis for GRP (Example 4, pages 33-34); measurement of blood pressure in vivo (Example 5, page 35); cord formation assay (Example 6, page 35); directed in vivo angiogenesis assay (Example 7, page 36) and proliferation assays of the lung cancer cell line H1299 with administration of the elected compound as well as a xenograft lung cancer model (Examples 8 and 9, pages 36-37).

The present claims circumscribe a method for treating any type of cancer cell or tumor by inhibiting GRP by administering the elected compound. That is, in order to be enabled to practice the elected invention, the skilled artisan would have to accept that by administering the presently claimed compound, all other tumors known in the art could be treated. In light of the fact that the specification not only fails to provide the skilled artisan with any direction or guidance as to how the treatment of any other cancer cell or tumor type, aside from lung cancer, could actually be achieved using the claimed combination, but also fails to direct the skilled artisan as to which other tumor types would be sensitive to this chemotherapeutic agent and how one would determine such sensitivity, the specification, which lacks an objective showing of which other tumors could be effectively treated using the claimed combination, is viewed as lacking an enabling disclosure of the entire scope of the claimed invention, especially in light of the highly complex nature of tumors and cancer in general.

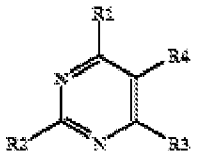
Here, the objective truth that any tumor type may be treated with the claimed compound is doubted because, while the state of the prior art of cancer treatment is well developed with regard to the treatment of specific cancer types with specific chemotherapeutic regiment (see Cecil's Textbook of Medicine, pages 1060-1074), the state of the art with regard to treating all tumors using a single agent is grossly underdeveloped.

In this regard, Cecil's Textbook of Medicine (2000) is cited. In particular, there is no known anticancer agent or combination of anticancer agents that is effective against treating all cancer types, nor is there any known anticancer agent or combination of agents that is effective against inhibiting the growth of any type of cancer cell. The Cecil reference clearly shows that for the various known cancer types, there is not one specific chemotherapeutic agent or combination thereof that is effective at treating cancer or inhibiting the growth of cancer cells for each and every type of cancer (see Table 198-5 at page 1065; Tables 198-6 and 198-7 at pages 1066; Table 198-8 at page 1068; and Table 198-9 at page 1071).

Given that there was not known any specific agent or combination of agents effective to treat all known type of cancer cells or tumors, one of ordinary skill in the art would not accept on its face Applicant's statement that such an objective could be achieved in any type of cancer cell or tumor using the presently claimed compound without enabling a set of species representative of full scope of cancers known in the art. The artisan would have required sufficient direction as to how, at minimum, a representative set of species for cancer could be effectively treated with the compound and, further, how the artisan could have reasonably extrapolated such results to the larger and highly varied genus of cancer cells and/or tumors in general would actually show sensitivity to the presently claimed compound, such that the artisan would have been imbued with at least a reasonable expectation of success in treating the cancer. Such success would not have been reasonably expected for all cancer cell and/or tumor types claimed given the highly complex and variable nature of all cancers known in the art and that Applicant has shown examples only in non small cell lung tumor cells. To the artisan, the concept of a single agent

effect to treat this subset of cancer types would not have been considered representative or suggestive of the same efficacy in the treatment of all known types of cancer cells and/or tumors in the absence of any evidence or reasoning to do so. Additionally, since the skilled artisan would have expected in the interaction of a particular agent in the treatment of a particular disease state to be very specific and highly unpredictable absent a clear understanding of the structural and biochemical basis for the use of each agent, one of skill in the art would have no other recourse but undue experimentation to undertake extensive testing to determine which other cancer cell and/or tumor types would be amendable to treatment using the claimed compound.

The prior art teaches that compounds with the core:



are known for the prophylaxis and treatment of diseases in a host caused by infection by rotaviruses (see abstract and claim 3 of Hisaki et al.; U.S. 6,080,750).

Notably, the purported effect and/or specific interaction of the inhibition of GRP with the instantly claimed compound and further the treatment of diseases with the inhibition of GRP, is never described within the four corners of the instant specification. The specification fails to present either view a working or prophetic example(s) or a clear, scientifically sound explanation as to what, in fact, enables (1) inhibition of GRP activity and (2) treating conditions associated with inhibition of GRP, specifically treatment of cellular proliferative diseases, such that the skilled artisan would have been imbued with at least a reasonable expectation of predictability of action in using the instantly claimed compound for use in treating any one or more of the disorders disclosed as being responsive to such an effect.

Absent such guidance, the experimentation required, without needing to resort to random

speculation, what therapeutic amounts would be available to even start testing for a therapeutic effect, would clearly be undue. Further, it is noted that, while the lack of a working embodiment cannot be the *sole* factor in determining enablement, the absence of substantial evidence commensurate in scope with the breadth of the presently claimed subject matter, in light of the unpredictable nature of the chemical and pharmaceutical arts and the limited direction that Applicant has presented, provides additional weight to the present conclusion of insufficient enablement in consideration of the *Wands* factors as a whole.

As stated in MPEP §2164.04[R-1], "Doubt may arise about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation." In the instant case, the information that is missing is a clear correlation between the claimed compound and its efficacy in inhibiting GRP, either through specific evidence in the form of data demonstrating such a fact or at least a sound mechanistic correlation between the claimed compound, *its ability to function in such a manner* and the amenability of the claimed disease state to treatment using an agent capable of functioning in this manner. In the absence of this information, the specification fails to provide adequate guidance and/or direction to one of skill in the art at the time of the invention that would have enabled such a person to practice the instantly claimed invention without having to resort to undue experimentation to determine how, in fact, one would achieve the instantly disclosed therapeutic objective(s).

The basis for the present rejection is not simply that experimentation would be required, since it is clear from the state of the prior art and Applicant's disclosure and remarks that experimentation in this particular art is not at all uncommon, but that the experimentation required in order to practice the full scope of the invention would be *undue*. Please reference *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states, "The test of enablement is not whether any experimentation is necessary, but whether, *if experimentation is necessary, it is undue*." (emphasis added) Accordingly, in the absence of any adequate disclosure, direction or guidance as to how one would go about using the

instantly claimed compound with a reasonable expectation of successfully treating the disclosed disorder(s), it remains that the pharmaceutical, chemical and medical arts are notoriously complex such that methods of use would have been sufficiently unpredictable to warrant the need for undue experimentation to actually practice the full scope of the invention as instantly claimed.

In view of the discussion of each of the preceding seven factors, the level of skill in the art is high and is at least that of a medical doctor or scientist with several years of experience in the art.

As the cited art and discussion of the above factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation or ability to make and use the full scope of the invention as instantly claimed, given the disclosure and supporting examples provided in the present specification and the state of the art at the time of the invention. In order to actually achieve the claimed invention, it is clear from the discussion above that the skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. 112, first paragraph, and would have no alternative recourse but the impermissible burden of undue experimentation in order to practice the full scope of the embodiments presently claimed.

Response to Applicant's Remarks

Applicant alleges that while the specification defines modulating as either stimulatory or inhibitory activity, the pending claims relate to the inhibition of GRP activity. Applicant alleges that the inhibition of GRP therefore leads to the treatment of conditions associated with GRP activity. Further, Applicant has guided the Examiner to page 17, lines 17-25 that the instant compound interferes with the binding of GRP to a GRP neutralizing antibody and further that the instant compound *modulates* GRP activity (emphasis added). Though Applicant alleges that modulation is drawn to the inhibition of GRP, by Applicant's own admission (page 8 of the response), the definition of modulating includes both stimulation and inhibition of GRP, supports the rejection in that the specification does not definitively set forth that the elected compound in fact inhibits GRP. Further, it should be noted that the cited passage

found on page 20, lines 3-10, states that "GRP-interfering small molecules by themselves did not produce any change in IP3 levels (line 7). Therefore, it seems that the modulation (whether that is stimulation or inhibition) does not change an activity of GRP. With regard to the interfering with binding of GRP antibody to GRP, the paragraph cited seems to summarize the findings of Chaundry et al. This reference does not seem to disclose the elected compound, but rather guides the practitioner on how to discriminate between target molecules. Applicant goes on to cited several different articles in support that a causal effect exists between the inhibition of GRP and the treatment of several different conditions and disorders. Given that as stated above, it does not seem that the instant specification sets forth that the elected compound in fact inhibits GRP, arguments and data on how this inhibition leads to the inhibition of an activity of GRP which thereby treats different disorders or diseases is not found persuasive.

Conclusion

No claim is found to be allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNA PAGONAKIS whose telephone number is (571)270-3505. The examiner can normally be reached on Monday thru Thursday, 9am to 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AP

/Brandon J Fetterolf/
Primary Examiner, Art Unit 1642